PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P045563PCT DBO/jdo	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NL2004/000006	International filing date *(day/month/year)* 07.01.2004	Priority date *(day/month/year)* 07.01.2003
International Patent Classification (IPC) or national classification and IPC A23L1/305		
Applicant N.V. NUTRICIA et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.04.2004	21.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Krajewski, D Telephone No. +49 89 2399-8472

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2004/000006

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-13 as originally filed

   Claims, Numbers

   1-20 received on 09.08.2004 with letter of 09.08.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-20
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11-20
	No:	Claims	1-9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	11-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Ad I.:

1. With letter dated 9.8.2004, the applicant has replaced the feature "improving nutrient utilisation" by the feature "suppressing feelings of satiety" in claim 1. Basis was given on p. 2, l. 1-4; p. 5, l. 6-8; p. 13, l. 5-6. In the opinion of the IPEA, these passages do not serve as a basis for said amendment. The first passage is a general description of symptoms related to delayed gastric emptying. The second passage discloses that significant amounts of GMP may induce feelings of satiety which effectively counteracts the advantageous effect resulting from the administration of lactoferrin. Lactoferrin is related in the whole application as being effective to reducing the residence time of nutrients in the stomach not to satiety (see eg. p. 4, l. 8-16). The last passage relates to the administration of a specific nutrient composition to patients and discloses that the patients of one group have a better nutrient utilisation and "are less prone to feelings of satiety". Being less prone is different from having suppressed feelings of satiety. Moreover, the recited effect is related to the administrated composition as a whole and not to lactoferrin alone.

   As set out above, the amendment as filed has no basis in the application as filed and the report is established as if the such amendment had not been made on the application as originally filed (Art. 34(2)(a) and R. 70.2(c) PCT).

2. The other amendments find basis in the originally filed documents.

Ad II.:

1. The feature "the weight ration of lactoferrin to ß-lactoglobulin exceeds 1 to 15" has no basis in the priority documents. Therefore, the priority is only validly claimed for claim 11 and claims being dependent thereupon but not incorporating the subject-matter of claim 12.

Ad V.:

1. Reference is made to the following documents:

   D1: WO 01/89553 A (SPILBURG CURTIS A ;STENSON WILLIAM F (US); BARNES JEWISH HOSPITAL) 29 November 2001 (2001-11-29)
   D2: US 2002/119928 A1 (MCANALLEY BILL H) 29 August 2002 (2002-08-29)
   D3: US 2001/009681 A1 (COCKRUM RICHARD H ET AL) 26 July 2001 (2001-07-26)

D4: WO 02/40013 A (SIGMA TAU HEALTHSCIENCE SPA ;POLA PIETRO (IT)) 23 May 2002 (2002-05-23)

D5: EP-A-0 295 009 (BAYLOR COLLEGE MEDICINE) 14 December 1988 (1988-12-14) cited in the application

D6: WO 02/15719 A (NESTLE SA) 28 February 2002 (2002-02-28) cited in the application

D7: PATENT ABSTRACTS OF JAPAN vol. 2003, no. 09, 3 September 2003 (2003-09-03) & JP 2003 137808 A (KAKUNAI JUYOTAI KENKYUSHO:KK), 14 May 2003 (2003-05-14)

D8: US 2002/016289 A1 (CONNEELY ORLA M ET AL) 7 February 2002 (2002-02-07)

D9: WO 98/50076 A (KRUZEL MARIAN L ;UNIV TEXAS (US); CASTRO GILBERT A (US)) 12 November 1998 (1998-11-12) cited in the application

D10: WO 99/64022 A (CRUM ALBERT B ;ZIVKOVIC D DOROTHY (US)) 16 December 1999 (1999-12-16)

D11: FR-A-2 296 428 (BAIGNES STE RADEGONDE LAITERIE) 30 July 1976 (1976-07-30) cited in the application

D12: TROOST FREDDY J ET AL: 'Gastric digestion of bovine lactoferrin in vivo in adults.' JOURNAL OF NUTRITION, vol. 131, no. 8, August 2001 (2001-08), pages 2101-2104, XP002241917 ISSN: 0022-3166

D13: DATABASE FSTA [Online] INTERNATIONAL FOOD INFORMATION SERVICE (IFIS), FRANFURT/MAIN, DE; SUZUKI T ET AL: 'Lactoferrin contents in bovine colostrum and milk.' Database accession no. 79-1-06-p0898 XP002278659 & JOURNAL OF THE JAPANESE SOCIETY OF FOOD AND NUTRITION ((EIYO TO SHOKURYO)) 1977 CENT. RES. LAB., MORINAGA MILK IND. CO. LTD., MEGURO-KU, TOKYO, JAPAN, vol. 30, no. 5, pages 317-322,

2. Claim 1 and claims depending thereupon

Claim 1 relates to the oral use of lactoferrin in the manufacture of a nutritional composition for improving the nutrient utilisation by a mammal. The composition is applied orally. The amount of lactoferrin used in a composition is not defined but should be such to reduce the residence time of nutrients in the stomach. Possible amounts according to the invention are 0.05, 0.2%, 0.4% or more (claims 2 and 3). The composition moreover has to contain ß-lactoglobulin with a lactoferrin to ß-lactoglobulin ratio that exceeds 1:15.

2.1 Novelty (Art. 33(2) PCT)

The subject-matter of claim 1-9 is anticipated by D1 - D5 (relevant passages see search report).

In all documents nutritional compositions with the content indicated in claims 2 or 3 is administered to mammals. All documents report better resorption of single nutrients or the entire food, weight gain or recovery from conditions do to administration of the composition where resorption was impaired. All the cited documents contain either bovine milk, milk derivates or colostrum supplemented with additional lactoferrin. Thus ß-lactoglobulin and glycomacropeptide are contained.

D1 discloses the improved digestibility of long chain triglycerides by human lactoferrin. One preferred embodiment is lactoferrin supplemented milk. The amount of supplementation corresponds to the lactoferrin content of human colostrum. D1 thus anticipates the subject-matter of claims 1-5,7,8,9.

D2 discloses supplements comprising bovine colostrum and lactoferrin. The supplement improves inter alia glucose utilization, resistance to toxin-related activities and athletic performance (par. 51). D2 thus anticipates the subject-matter of claims 1-3,8,9,10. The same analysis applies to D3 (D3 anticipates the subject-matter of claims 1-3, 8, 9).

D4 discloses improved iron utilisation or immunostimulation do to ingestion of a lactoferrin, carnitin, colostrum supplemented health food. The subject-matter of claims 1-4,6 is anticipated.

D5 reports the reduction of chronic diarrhea in human or nonhuman infants. Thus nutrient resorption is reduced. A newborn suffering from this condition will be under medical treatment and be treated with medicaments, thus will be under chemotherapy. Milk based infant food is supplemented with lactoferrin occurring in human colostrum. A bovine milk based food supplemented with an amount of 3g/l lactoferrin will anticipate the subject-matter of claims 1-5,7,8,9.

2.2 Inventive step (Art. 33(3) PCT)

The methods of claims 5,7,8-10 are directly derivable for the skilled person from

the teaching of D4.

3. Claim 11 and claims depending thereupon

3.1 Novelty (Art. 33(2) PCT)

Claim 11 relates to a nutritional composition having a specific composition. D6 differs in the lactoferrin content of the composition. D11 exhibits the same caloric distribution as D6 but contains less proteins per liter beverage.
The subject-matter of claims 11-20 is thus new.

3.2 Inventive step (Art. 33(3) PCT)

D6 and the composition of the present invention differ in that in D6 whey is not additionally supplemented with lactoferrin.
D11 teaches that the administration of the composition comprising whey helps to improve appetite, recover from an illness, or surgery and chronic gastritis. A composition more or less corresponding to the composition of bovine whey (D11) is disclosed to help in the recovery from digestive problems and improve nutrient absorption. Bovine whey contains lactoferrin in a minor amount.

In the present application, lactoferrin helps to improve nutrient utilisation. Gastric emptying is increased and thus patients with irritable bowel syndrome, functional dyspepsia etc. can absorb more nutrients.

The effect achieved by the additional supplementation with lactoferrin is regarded to further improve nutrient utilisation in view of D6 by a patient suffering from digestive problems such as patients suffering from chronic gastritis or ulcers (D6, see p. 1, l. 8-15; p. 6, l. 11-17).
Lactoferrin is known to help in the treatment of inflammatory illnesses such as gastritis (D8) or to improve nutrient absorptions in individuals (see eg D4, D5).
Furthermore, D7 teaches the supplementation of enteral compositions with lactoferrin in order to improve the recovery of patients suffering from an operation or suffering from mucous membrane disorders (D7 is relevant for those claims not being covered by a priority).
Thus a supplementation with lactoferrin in the indicated amount is thus an obvious choice for the skilled person intending to improve the composition of D6.

The subject-matter of claims 11-20 thus does not involve an inventive step.

4. Industrial applicability (Art. 33(4) PCT)

For the assessment of the present claims 1-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 11-20 fulfill the requirements of Art. 33(4) PCT.

CLAIMS

1. Use of lactoferrin in the manufacture of a nutritional composition for use in a method of ~~improving nutrient utilisation by~~suppressing feelings of satiety in a mammal ~~in need thereof~~, wherein the method comprises orally administering the lactoferrin containing composition in an amount effective to reduce the residence time of nutrients in the stomach of the mammal, said composition exhibiting a weight ratio of lactoferrin to β-lactoglobulin that exceeds 1 to 15.

2. Use according to claim 1, wherein the method comprises administering a nutritional composition containing at least 0.2 wt.%, preferably at least 0.4 wt.% lactoferrin.

3. Use according to claim 1, wherein the method comprises administering a nutritional composition containing at least 0.05 wt.% lactoferrin and 0-0.15 wt.% glycomacropeptide.

4. Use according to any one of the preceding claims, wherein the method comprises administering lactoferrin in a dosage of at least 0.1 g, preferably of at least 0.2 g.

5. Use according to claim 1 or 2, wherein the method comprises administering a pourable nutritional composition having a caloric content of at least 1 kcal/ml and a viscosity of 100 mPa.s or less at 21 °C.

6. Use according to any one of the preceding claims, wherein the method comprises co-administering a carnitine source in an amount equivalent to at least 10 mg L-carnitine, preferably in an amount equivelent to between 10 mg and 75 mg L-carnitine.

7. Use according to any one of the preceding claims, wherein the nutritional composition is administered in an amount of 20-400 ml, preferably of 100-250 ml

8. Use according to any one of the preceding claims, wherein the mammal is a hospitalised patient or wherein the mammal suffers from impaired gastric motility.

9. Use according to any one of the preceding claims, wherein the mammal is a patient undergoing chemotherapy.

10. Use according to any one of the preceding claims, wherein the nutritional composition is consumed within 1 hour prior to or during physical exercise.

11. A pourable artificial nutritional composition that has a caloric content of at least 1.0 kcal/ml, a viscosity of 100 mPa.s or less at 21 °C and that comprises:

a 50-79.6 wt.% water;

b at least 0.4 wt.%, preferably 0.6-5 wt.% lactoferrin

c 1-30 wt.%, preferably 1-20 wt.%, more preferably 7-12 wt.% proteinaceous matter other than lactoferrin;

d 0.1-20 wt.%, preferably 3-10 wt.% lipids;

e 10-30 wt.%, preferably 10-20 wt.% carbohydrates;

wherein the combination of these components constitutes at least 80 wt.% of the composition and the proteinaceous matter, lipids and/or carbohydrates together constitute at least 20 wt.% of the composition.

12. Nutritional composition according to claim 11, wherein the weight ratio of lactoferrin to β-lactoglobulin exceeds 1 to 15.

13. Nutritional composition according to claim 11 or 12, wherein not more than 10 wt.% of the proteinaceous matter is hydrolysed protein.

14. Nutritional composition according to any one of claims 11-13, wherein the lipids and the carbohydrates together constitute at least 13 wt.%, preferably at least 18 wt.%, most preferably 22 wt.% of the composition.

15. Nutritional composition according to any one of claims 11-14, wherein the nutritional composition contains at least 5 wt.%, preferably 10-50 wt.% ω–3-fatty acids (including ω–3-fatty acid residues) by weight of the total amount of lipids.

16. Nutritional composition according to any one of claims 11-15, wherein the nutritional composition contains ω-~~3~~6-fatty acid residues and ω-~~6~~3-fatty acid residues in a weight ratio between 6:1 and 1:3.

17. Nutritional composition according to any one of claims 11-16, wherein the nutritional composition contains at least 5 wt.%, preferably 10-90 wt.% C_8-C_{14} fatty acids (including C_8-C_{14} fatty acid residues) by weight of the total amount of fatty acids.

18. Nutritional composition according to any one of claims 11-17, wherein the nutritional composition contains at least 10 wt.% of carbohydrates with a glycemic index of less than 80.

19. Nutritional composition according to any one of claims 11-18, wherein the nutrional composition contains at least 0.015 wt.%, preferably between 0.02 and 0.045 wt.% carnitine.

20. Packaged artificial nutritional product comprising 20-400 ml, preferably of 100-250 ml of a nutritional composition according to any one of claims 11-19.